Developing treatments for prevention of retinopathy of prematurity

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"Retinopathy of prematurity clinical trials have focused more on mitigating retinopathy of prematurity progression ... than prevention."

Retinopathy of prematurity (ROP) develops in half of the preterm infants born prior to 28 weeks gestational age (GA) and is up to 20 times more likely to occur in infants born before 25 weeks GA than those born after 28 weeks. ROP risk at 23 weeks is double that at 25 weeks GA [1–4]. Infants born prior to 28 weeks are also at greater risk for more severe ROP. Owing to the fact that twice as many extremely low birth weight infants (<1000 g) are surviving as compared with 20 years ago, the population at highest risk for developing severe ROP has been increasing [5–7].

Starting at 15 weeks in human fetal retinas, the first event in retinal vascularization (formation of primordial vessels in the central retina) is mediated by vasculogenesis [8]. By 25–26 weeks, angiogenesis is occurring in the inner retina through increasing vascular density and peripheral vascularization and in the outer plexus by extension of capillary-sized buds from existing inner vessels. ROP pathophysiology occurs in two successive phases [9,10]. First, in the developing posterior retina, vascular growth takes place under the influence of *in utero* hypoxia and upregulation of VEGF. After premature birth, this process is inhibited by hyperoxia (even supraphysiologic room air), the absence of autoregulation of retinal blood flow and a relative deficiency of antioxidants in the immature retina. In the absence of sufficient VEGF, IGF1 and other factors, angiogenic budding stops and developing vessels involute. The second phase occurs following birth as the avascular, anterior retina grows and becomes more metabolically active. Infants with the lowest GA and who, therefore, have the most immature vascularization patterns are most at risk, with the resulting local tissue hypoxia stimulating increased release of VEGF and an abnormal neovascularization.

Hyperoxia, hypoxia and increased reactive oxygen species (ROS) are integral to the development of ROP [11,12]. A delicate balance exists between the production of ROS and the antioxidant defenses that protect each cell. Premature infants are delayed in their development of antioxidant protection systems and are thus more susceptible to ROS-induced damage of cellular components [13]. ROS are also molecular signals in the regulation of genes involved in angiogenesis (e.g., VEGF) and control of vascular tone (e.g., nitric oxide synthase) [14].

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Bovine retinal epithelial cells exposed to hyperoxia in culture undergo apoptosis, a process that is dependent on the generation of ROS and reactive nitrogen species (e.g., superoxide, peroxynitrite) [15]. Cell survival under hyperoxia was significantly increased by pretreatment with antioxidants such as superoxide dismutase (SOD); this is consistent with previous *in vitro* and newborn animal studies, demonstrating that exposure to hyperoxia and nitric oxide can cause peroxynitrite formation, lung epithelial cell damage and

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significant lung injury. Prophylactic administration of recombinant human Cu/Zn SOD (rhSOD) prevented peroxynitrite formation and reduced cell damage and lung injury.

In a newborn piglet model, intratracheal rhSOD prevented hyperoxic lung injury [16]. Within 30 minutes of administration, labelled rhSOD was taken up by multiple pulmonary cell types, after which it was absorbed into the bloodstream and excreted in the urine. Phase I rhSOD studies in preterm infants receiving single or multiple doses revealed serum SOD levels increase by up to three- to fivefold within 6 h and remain elevated for up to 48 h [17]. Increased circulating SOD levels could potentially impact vascular beds remote from the lung. Although supplemental antioxidants may reduce cellular and tissue injury in multiple organs, it is not clear whether scavenging ROS help by diminishing direct injury or inhibiting upregulation of potentially harmful cell signaling pathways.

ROP clinical trials have focused more on mitigating ROP progression (e.g., Cryotherapy for ROP, Supplemental Therapeutic Oxygen for Prethreshold ROP and Early Treatment for ROP) than prevention [4]. Reducing inspired oxygen concentrations and administering antioxidants may reduce ROP risk and severity in low GA infants [1,11,18,19]. Although a meta-analysis of six randomized trials administering vitamin E to preterm infants concluded that there was a 50% reduction in severe ROP [20], the dose required for protection was associated with an increased risk of sepsis and necrotizing enterocolitis [21]. D-Penicillamine was also suggested to lower ROP incidence in preterm infants [22]. Randomized trials of IGF1 and long chain polyunsaturated fatty acids supplementation are currently underway [23].

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In a multicenter trial of intratracheal rhSOD for prevention of bronchopulmonary dysplasia, 302 preterm infants were randomized to receive intratracheal rhSOD or placebo at birth and every 48 h for 28 days. The initial analysis failed to demonstrate any impact on ROP incidence. However, armed with the more recent data reviewed above, the data were re-examined to assess subcohorts <26 weeks' GA with the hypothesis that lower GA infants should have the highest risk and may demonstrate a larger effect [24,25]. This reanalysis confirmed that risk and severity increased with decreasing GA. While in the entire cohort, no significant differences in ROP were found in the placebo versus rhSOD group, subgroup analysis on infants born at <25 weeks (n = 24) showed ROP reduced by 53% from 85% (placebo) to 40% (rhSOD; p = 0.03). ROP severity above stage 2 was found in 42% of placebo-treated infants, but only 25% of those subjects treated with rhSOD, suggesting rhSOD could reduce the risk of developing ROP in extremely low gestational age newborns (ELGANs). The effects of rhSOD on the developing retina may be similar to effects seen in the lung, where rhSOD reduces cell injury and death by diminishing direct ROS-induced injury as well as preventing upregulation of important pro-death signaling pathways within the cell.

Where do we stand now? Results from the SUPPORT trial [26] caution that while maintaining lower oxygen saturation may reduce the risk of ROP, the associated cost is an increased risk in mortality; an unacceptable tradeoff. Although there are therapeutic options for established ROP [23,27], the preferable course of action, were medications or clinical strategies available, would be prevention of ROP from occurring or at least attenuation of severity. Through development of potential prevention strategies such as rhSOD and IGF1, it may be possible to stem the tide of increasing numbers of high ROP-risk ELGANs who will be managed with higher oxygen saturation thresholds. An appropriately powered randomized clinical trial is needed to determine whether rhSOD reduces the incidence of ROP and other ROS-mediated disease processes in ELGANs.

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